

### REMARKS

Claims 1-38 and 40 are currently pending. Claims 1, 4-7, 9, and 14 are amended herein to clarify the claimed subject matter. Claim 3 is canceled herein without prejudice. Accordingly, instant claims 1-2, 4-38, and 40 are under consideration.

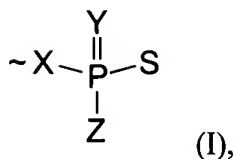
Any amendment, however, is not to be construed as abandonment of any subject matter of the originally filed application. Accordingly, it is to be understood that Applicant reserves the right to reintroduce subject matter deleted from the application by the foregoing amendments and to file one or more divisional, continuation, and/or continuation in part applications directed to such subject matter.

Support for amendment to the claims is found throughout the specification and in the original claims. More specifically, support for amendment to claim 1 is found, for example, in original claim 3 and at page 4, lines 22-34; at page 7, line 29 through to page 8, line 17; and in Figure 1. Support for amendment to claims 4-7, whereby dependency recited therein is amended, is found, for example, in original claims 1 and 3. Support for amendment to claim 9 is found, for example, in original claim 7. Claim 14 is amended to correct a clerical error. No issue of new matter is introduced by these amendments.

### ***Rejections under 35 USC § 102***

Claims 1 and 2 are rejected under § 102(b) as allegedly anticipated by Lane et al. (WO 97/08183). Claim 1 is amended herein to clarify the subject matter of the claim. In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

More particularly, claim 1 is amended herein to be directed to a hairpin polynucleotide, having a loop and a stem region, characterised in that the hairpin polynucleotide comprises a sulfur-based nucleophile, wherein the sulfur-based nucleophile is a moiety of the formula (I):



wherein ~ denotes the bond or linker connecting the sulfur-based nucleophile to the remainder of the polynucleotide; X represents an oxygen atom, a sulfur atom or a group NR, in which R is hydrogen or an optionally substituted C<sub>1-10</sub> alkyl; Y represents an oxygen or a sulfur atom; and Z represents an oxygen atom, a sulfur atom or an optionally substituted C<sub>1-10</sub> alkyl group, and wherein the sulfur-based nucleophile is attached to an internal nucleotide in the hairpin through a linker to enable binding to a solid support. Thus, the instant hairpin polynucleotide comprises a sulfur-phosphorus linkage. In contrast, Lane et al. teach a sulfhydryl functionalised hairpin. Lane et al., furthermore, fail to teach or suggest a hairpin polynucleotide that comprises a sulfur-phosphorus linkage. In that the instant claims are amended to specify that the hairpin polynucleotides of the present invention possess features that are not taught or suggested by Lane et al., namely a hairpin polynucleotide that comprises a sulfur-phosphorus linkage, Applicant asserts that WO 97/08183 fails to anticipate the claimed molecules.

In view of the amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-2 under 35 U.S.C. §102 and withdraw the rejection.

The Examiner has rejected claims 1-9, 15, 18-20, 23-34, 37, 38, and 40 under 35 U.S.C. §102(b) as allegedly anticipated by Zhao et al. (Nucleic Acids Research, 2001, 29:955-959). As indicated above, claim 1 is amended herein to clarify the subject matter of the claim. Claims 4-7 and 9 are amended to alter dependency recited therein. Claim 3 is canceled herein, thereby obviating any rejection of this claim. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection as it applied to claims 1-9, 15, 18-20, 23-34, 37, 38, and 40 is respectfully traversed.

As indicated herein above, the hairpin polynucleotide of claim 1 comprises a sulfur-phosphorus linkage. In contrast, the Zhao et al. reference teaches a hairpin polynucleotide that is

covalently immobilised to a solid support through a sulfur atom, wherein the sulfur atom is in the form of a sterically hindered backbone modified thiophosphate without a linker moiety. That being the case, Zhao et al. is directed to a hairpin polynucleotide that is structurally distinct from the hairpin polynucleotides of the present invention. Zhao et al., therefore, fails to teach or suggest a recited feature of the instant hairpin polynucleotides because this reference fails to teach or suggest a hairpin polynucleotide that comprises a sulfur-phosphorus linkage, wherein the sulfur-based nucleophile is attached to an internal nucleotide in the hairpin through a linker.

In view of the amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-9, 15, 18-20, 23-34, 37, 38, and 40 under 35 U.S.C. §102 and withdraw the rejection.

### ***Rejections under 35 USC § 103***

Claims 1-9, 11-12, 15-38, and 40 are rejected under § 103(a) as allegedly unpatentable over Balasubramanian et al. (U.S. Patent Application Serial Number 2003/0022207) in view of Zhao et al. (Nucleic Acids Research, 2001, 29:955-959). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

As detailed above, claim 1 is amended herein to clarify that the claimed hairpin polynucleotides are thiophosphate analogs as shown in formula (I), wherein the thiophosphate moiety/moieties are positioned on the end of a linker. Neither Balasubramanian et al. or Zhao et al., when considered alone or in combination, teaches or suggests such a thiophosphate analog, wherein the thiophosphate moiety/moieties are positioned on the end of a linker as presently claimed. In light of the above, the combined teachings of the cited references fail to teach or suggest each and every element of the hairpin polynucleotides of claim 1 and, therefore, fail to render obvious the instant claims.

Moreover, the absence of any guidance in these references relating to thiophosphate analogs as depicted in formula (I), wherein the thiophosphate moiety/moieties are located on the end of a linker, underscores a total lack of appreciation regarding any potential advantages of

positioning a thiophosphate moiety/moieties in such a manner. Briefly, the Zhao et al. reference describes attachment of hairpin stem-loop structures with multiple phosphorothioate moieties in the loop to a solid support. The Examiner acknowledges this structural limitation of the hairpin oligonucleotides of Zhao et al. by describing the oligonucleotides as modified with multiple phosphorothioates in their backbone. As further described therein, during the process of hybridizing an oligonucleotide to another oligonucleotide already coupled to the surface, "The loop and stem presumably serve as lateral spacers between neighboring oligodeoxyribonucleotides and as a linker arm between the glass surface and the single-stranded sequence of interest." and thus, might be expected to aid hybridization. See, for example, the Abstract of Zhao et al. The phosphorothioate groups in the hairpin loops of Zhao et al. are, therefore, utilized as means for direct attachment to the surface. There is, however, no suggestion in Zhao et al. to indicate that the use of a separate linker to connect the phosphorothioate group to the polynucleotide can improve the efficiency of the initial covalent coupling reaction that couples the hairpin polynucleotide to the chemically functionalized solid support.

The limited efficiency of coupling hairpin oligonucleotides such as those described by Zhao et al. to a chemically functionalized solid support is revealed, for example, in Figure 2 of the instant application. More particularly, the experimental results of the present invention reveal that the efficiency of attachment of thiophosphate modified hairpin polynucleotides to a solid support is dramatically improved when the thiophosphate moiety is attached through a linker rather than simply placed in the backbone chain of the polynucleotide. The difference in coupling efficiency is depicted in Figure 2, wherein spot A shows a high level of signal from an immobilized hairpin polynucleotide containing the internal sulfur based nucleophile in the form of a thiophosphate moiety on the end of a linker (the novel hairpin oligonucleotide of the present invention), and spot B shows a significantly lower signal from a polynucleotide containing the sulfur based nucleophile in the form of a more sterically hindered phosphorothioate backbone modification (such as the hairpin oligonucleotide of Zhao et al.). Moreover, as stated in the

present specification, the discovery that the novel hairpin nucleotides of the present invention possess substantially enhanced attachment efficiency was surprising. See, for example, the Summary and Examples of the present specification.

In light of the above, the combined teachings of Balasubramanian et al. and Zhao et al. fail to teach or suggest a recited feature of the instantly claimed hairpin polynucleotides and furthermore, fail to have any appreciation for the surprising and useful properties conferred by this feature. More particularly, the combined teachings of Balasubramanian et al. and Zhao et al. fail to provide any guidance relating to the claimed hairpin polynucleotides, which are thiophosphate analogs as depicted in formula (I), wherein the thiophosphate moiety/moieties are positioned on the end of a linker. These references also fail to teach or suggest that the claimed hairpins would possess a novel and surprising functional property, namely improved coupling efficiency to a chemically functionalized solid support. That being the case, the combined teachings of Balasubramanian et al. and Zhao et al. fail to teach each and every element of the instant claims and functional properties conferred by inclusion of such elements and, therefore, would not lead an ordinarily skilled practitioner to the presently claimed invention.

In view of the amendments to the claims and the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-9, 11-12, 15-38, and 40 under 35 U.S.C. §103 and withdraw the rejection.

### ***Fees***


No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

### ***Conclusion***

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there

are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

  
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